DIFFERENTIATION OF INTESTINAL TUBERCULOSIS FROM CROHN'S DISEASE: ROLE OF COLONOSCOPY

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DECLARATION

I, **Dr.P.RAJESH PRABHU,** solemnly declare that the dissertation titled, **"DIFFERENTIATION OF INTESTINAL TUBERCULOSIS FROM CROHN'S DISEASE: ROLE OF COLONOSCOPY "** is a bona fide work done by me at Govt. Stanley Medical College and Hospital during the period January 2006 to December 2007.

This dissertation is submitted to the **TamilNadu Dr.MGR Medical University** towards partial fulfillment of the regulations for the award of **D.M Degree (Branch IV) in Medical Gastroenterology.**

Place : Chennai

Date : 02.06.08 Dr.P.RAJESH PRABHU

CERTIFICATE

This is to certify that this dissertation entitled **"DIFFERENTIATION OF INTESTINAL TUBERCULOSIS FROM CROHN'S DISEASE: ROLE OF COLONOSCOPY "** is a bona fide original work done by **Dr.P.RAJESH PRABHU,** in partial fulfillment of the regulations for the award of the degree of **D.M (Branch IV) Medical Gastroenterology** examination conducted by the Tamil Nadu Dr.MGR Medical University to be held in August 2008.

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TABLE OF CONTENTS

INTRODUCTION

The tuberculosis epidemic is expanding and currently a third of the world's population is infected, the majority residing in the developing world.[1] The epidemiology of IBD is also changing, though far less dramatically, with more cases from low and middle income countries being reported. There exists a multifaceted relationship between intestinal tuberculosis (ITB) and Crohn's disease (CD), as they share common pathogenic and clinical characteristics and were thought to be one in the same disease.

The interface between these two diseases is particularly relevant in the developing world where tuberculosis complicates both the diagnosis and management of CD. Eighty per cent of all new cases in 2004 occurred in Africa, South-East Asia and Western Pacific regions[2] and several studies have shown an increasing incidence of extra-pulmonary TB.[3,4]

Recently drug resistant tuberculosis has been reported from 17 countries including the USA.[5] Mortality in this untreatable form of TB is almost 100%.[6] In patients with active pulmonary tuberculosis concurrent ITB can occur in up to 46% of patients if the gastrointestinal tract is examined.[7] Autopsy studies have also shown that ITB often goes clinically undetected.[8]

Once considered rare in the developing world, the epidemiology of IBD is changing and the incidence of both CD and ulcerative colitis (UC) is increasing in the Asian Pacific region, India, Eastern Europe and South Africa.[9-11] This is heralded by an increase in the incidence of UC followed by CD 15-20 years later.[12]

Making a diagnosis of Inflammatory Bowel Disease (IBD) in developed countries is facilitated by a limited differential diagnosis and unrestricted access to endoscopy and abdominal imaging. Moreover, a range of therapeutic options, including costly biological therapies are available, well-developed healthcare infrastructure is in place and patients have ready access to information about their disease. In contrast IBD in the developing world is overshadowed by enteric infections and awareness of the condition, by both patient and clinician, is often limited.

In resource poor environments access to technology, such as endoscopy, is reduced making the diagnosis of IBD difficult. In those patients with an established diagnosis of IBD treatment is complicated by a high burden of infectious diseases, poorly developed healthcare infrastructure and barriers to accessing information. Furthermore, funding for IBD research in these environments is limited by competing healthcare needs.

AIMS OF THE STUDY

To identify the distinctive characteristics of ileocecal and colonic tuberculosis (TB) and Crohn's disease (CD) at colonoscopy and

1) To correlate the colonoscopic findings with histology

REVIEW OF LITERATURE

Crohn's disease (CD) and Tuberculosis (TB) are both chronic granulomatous conditions which affect the gastrointestinal tract in a similar manner. *Mycobacterium tuberculosis* is the causative organism in ITB whereas the etiology of CD is multi-factorial and includes genetic, immunological, environmental and microbial factors.

Tuberculosis, HIV and Crohn's Disease:

Intestinal TB and HIV co-infection varies from 0% in studies from Korea[37] and to 13% in an Indian study.[63] Although HIV is intimately linked to TB the HIV infected patient develops disseminated TB which manifests in the abdomen as ascites, lymphadenopathy and hepato-splenic disease, and is often smear negative. Confirming a diagnosis of abdominal TB in this clinical setting is difficult; however, the use of an expanded TB case definition and monitoring objective responses to anti-TB treatment has been used successfully as a diagnostic alternative in resource poor environments. In contrast ITB with a Crohn's-like phenotype is usually seen in the immunocompetent patient with a robust immune response and 'contained' infection. The diagnosis of CD in

an HIV infected patient should therefore only be made after very careful consideration. Conversely, established IBD patients in our environment are at risk of HIV infection commensurate with local prevalence patterns.

Immunopathogenesis:

Crohn's disease and TB are both chronic granulomatous conditions which affect the gastrointestinal tract in a similar manner. It is not surprising given striking morphological similarities that they share many common immune pathways of pathogenesis, nor that corticosteroids have been used effectively in both disorders to control deleterious inflammatory reactions.

Both the diseases trigger potent adaptive TH_1 cytokine responses which result in granuloma formation and are characterized by robust production of interferon-gamma (IFN-γ), IL-12 and IL-23.[13]

In contrast to the forceful adaptive immune responses seen, both CD and TB appear to be associated with impaired innate immunity.[14,15] Only 5-10% of patients infected with *M. tuberculosis* develop active tuberculosis. Furthermore, as with CD the protean manifestations of TB suggests that individual variation in host-bacterial interactions may contribute to disease phenotype and that host genetics may play a role in dictating the efficacy of innate immune responses.

Nucleotide-binding oligomerization domain-2 (*NOD2*) and Toll-like receptors

(*TLRs*) may play a role in the early, inductive stages of both diseases. NOD2 single nucleotide polymorphisms (*SNPs*) confer susceptibility to CD in certain populations.[16] The role of *Mycobacterium avium paratuberculosis (MAP)* in the causation of Crohn's disease has been debated with the possible explanation evoking the concept of molecular mimicry, with antibodies directed against mycobacterial antigen cross reacting with intestinal components. [17] Both TB and CD are characterized by enormous heterogeneity and it may be, as has been shown in CD, that polymorphisms predict disease phenotype.

There has been a longstanding debate on the role of *Mycobacterium avium paratuberculosis* (MAP) in CD, which remains unresolved. It has long been recognized that CD does not exist in germ-free environments and that luminal bacteria are required for the development of inflammation in animal models of IBD. The recognition of NOD2 gene mutations in enhancing susceptibility to CD has placed emphasis on the role of luminal microflora in this disorder. It is, however, overly simplistic to assume a true infectious causality of CD given the success of anti- tumour necrosis factor-α (TNF-α) therapies, which should markedly worsen the course of an active mycobacterial infection. As such if MAP plays a role, it is likely to be a little more esoteric. One possible explanation evokes the concept of molecular mimicry, with antibodies directed against mycobacterial antigen cross reacting with intestinal components.

Clinical presentation:

In developed nations, TB is a disease of immigrants, the indigent or institutionalized or occurs in the immunosuppressed. In areas of high-TB prevalence, the disease is of the young or middle-aged with no distinguishing demographics. Intuitively the duration of symptoms would seem a distinguishing feature, but both diseases have an insidious onset which may go undiagnosed for many years. Furthermore, ITB has been identified in patients undergoing colonoscopy who were either well or had trivial symptoms.

Both conditions are characterized by anorexia, loss of weight, abdominal pain, altered bowel habits, rectal bleeding or the presence of an abdominal mass.[18,19] More acute presentations with intestinal perforation or obstruction, or intra-abdominal abscess can also occur.[20] Rarely ITB may present with malabsorption and a protein losing enteropathy.[21] The site of involvement is also similar with a predilection for the ileo-caecal region but both can involve the gastrointestinal tract from the mouth to anus. Fever is seen in both CD and ITB, but a high-swinging fever (>38.5 °C) favours ITB in the absence of any intra-abdominal abscess.[22]

Smoking is an environmental factor associated with CD. Similarly there is an association between smoking and tuberculosis infection in high-incidence areas. This may be explained by the effect of cigarette smoke on pulmonary macrophage or dendritic cell function.[23] However, there is no evidence showing a direct relationship

between smoking and ITB.

Despite their morphological and immunopathogenic similarities, the natural history of these two conditions is divergent. TB is associated with significant morbidity and mortality[24] but can be cured with a 6-month course of anti-tuberculous chemotherapy. By contrast, CD is a chronic condition that tends to progress with time and may require lifelong therapy to maintain disease remission in the majority of patients.

In areas of high-TB prevalence, empiric treatment for TB with careful clinical review is often resorted to when diagnostic uncertainty exists. This approach is problematic as it may delay treatment for CD or make it difficult to confirm or refute a diagnosis of ITB at a later stage. Furthermore, severe adverse drug reactions to anti-tuberculous chemotherapy can complicate management with empiric therapy. Conversely treatment for CD may be disastrous if a diagnosis of intestinal TB was missed.

Clinical differentiation:

Despite their morphological and immunopathogenic similarities, the natural history of these two conditions is divergent. ITB is associated with significant morbidity and mortality, but can be cured with a 6-month course of anti-tuberculous

chemotherapy. By contrast, CD is a chronic condition that tends to progress with time and may require lifelong therapy to maintain disease remission in the majority of patients.

Differentiating CD from ITB is difficult and although diagnostic criteria for both diseases exist they are not mutually exclusive.[24, 25] Both diseases have similar clinical, radiological and endoscopic features and current methods of confirming a diagnosis have limitations. In areas of high-TB prevalence, empiric treatment for TB with careful clinical review is often resorted to when diagnostic uncertainty exists.[26]

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Similar to TB, a variety of extra-intestinal manifestations of CD have been described, including immunologically mediated reactive polyarthritis (Poncet's disease), erythema nodosum, erythema induratum, uveitis, and thrombo-embolic manifestations. [27] Fistulization is one of the clinical hallmarks of CD. However, entero-enteric, entero-cutaneous and peri-anal fistulas are all well described in intestinal TB.[28] Both Crohn's disease and ITB are associated with anaemia, leukocytosis, thrombocytosis, a low serum albumin and raised inflammatory markers and routine blood tests play no role in the differentiation of CD from ITB.

Extra-pulmonary TB is often associated with a normal chest radiograph[29] Very rarely Crohn's may involve the lung with features similar to PTB such as a milary pattern with granulomatous inflammation on transbronchial biopsy.[30] Thus, a normal chest x-ray does not exclude the diagnosis of intestinal TB and rarely CD may involve the lung.

The use of tuberculin skin testing (TST) as a diagnostic tool in patients with ileo-colonic inflammation has limitations. Cross reactivity with BCG, a high prevalence of environmental mycobacteria and widespread latent *M. tuberculosis* infection makes interpretation of a positive TST difficult. Anergy in HIV, primary TB and disseminated TB further limits the diagnostic utility of this test. Anergy has also been demonstrated in untreated CD patients.[31]

Colonoscopy:

Colonoscopy with intubation of the terminal ileum combined with endoscopic mucosal biopsy is required in the evaluation of any patient with suspected CD or ITB. The majority of ITB cases will involve the ileo-caecum with varying degrees of contiguous colon and small bowel involvement. In approximately 20% of cases, segmental colonic involvement occurs in the absence of ileo-caecal involvement[32,33] and lesions in greater than two colonic sites, so-called skip lesions, may occur in up to 44% of patients.[34] Approximately 5% will present with a pancolitis picture indistinguishable from UC.[32,33,35] Isolated small intestinal or upper gastrointestinal tract disease is also well described.[36] With the advent of endoscopy the type of lesion rather than the

distribution has become important in differentiating CD from ITB (Table 1). Morphologically, circumferential, transverse ulcers are more common in ITB (Fig 1) and linear, longitudinal ulcers are commonly seen in CD (Fig 2).

Lee and colleagues in the first systematic prospective analysis evaluated endoscopic findings in 44 patients with ITB and 44 patients with CD. A scoring system comprising four endoscopic features of CD (anorectal lesions, longitudinal ulcers, apthous ulcers, cobblestone appearance) vs. four endoscopic features of ITB (transverse ulcers, pseudopolyps, involvement of fewer than four segments and a patulous ileo-caecal valve) was used. With this method, a positive predictive value for CD of 94.9% and 88.9% for ITB was achieved.[37]

Table 1. Endoscopic Features of ITB and Crohn's Disease

Intestinal TB	**Crohn's disease**
Circumferential Ulcers	Longitudinal Ulcers
Surrounding mucosa inflamed/nodular	Surrounding mucosa normal
Apthous ulcers uncommon	Apthous ulcers common
Hyperaemic nodules-isolated or in clusters	Cobblestoning
Pseudopolyps	Multiple skip lesions
Hypertrophic mucosa	Anorectal lesions
Strictures	Strictures
Destruction of ICV and/or caecum	Preservation of ICV

Histopathology:

Differentiating ITB from CD in endemic areas poses a major challenge to pathologists as both conditions are characterized by granulomatous inflammation with overlapping histologic features. Many early comparisons between these conditions were based on resection specimens, in which the large sample size and availability of all layers of the bowel wall facilitated identification of pathognomonic lesions. However, many of these features are non-specific and even in resection specimens it can be difficult to tell ITB and CD apart.

In ITB, the classical and pathognomonic features of caseating granulomatous inflammation and acid fast bacilli are present in <30% of cases, with a < 20% yield of positive TB culture often delaying the diagnosis.[38] Retrospective studies from South India [39, 40] and South Africa[41] have identified a number of features that appear helpful in distinguishing CD from ITB in colonoscopic biopsies (Table 2).

The histopathological findings frequently seen in ITB are confluent granulomas, multiple granulomas in a given biopsy site, large granuloma size (Fig 3), bands of epithelioid histiocytes lining ulcers, submucosal granulomas and disproportionate submucosal inflammation, apart from caseous necrosis and acid fast bacilli.[39-41] Features seen far more frequently in CD include single granulomas (Fig 4), as the only foci of granulomatous inflammation and architectural distortion distant from granulomatous inflammation.[39]

Table 2. Prevalence of Selected Histological Parameters in Patients with Intestinal Tuberculosis (ITB) and Crohn's Disease (CD): A Comparison of Three Studies [39-41]

	Pulimood *et al.* (1999) South India		**Pulimood *et al.* (2005) South India**		**Kirsch *et al.* (2006) South Africa**	
	ITB (n=20)	*CD (n=20)*	*ITB (n=33)*	*CD (n=31)*	*ITB (n=18)*	*CD (n=25)*
Caseous necrosis	40	0	36	0	22	0
Confluent granulomas	60	0	42	3	50	0
≥5 granulomas/biopsy site	40	0	45	0	44	24
≥10 granulomas/biopsy site	--	--	--	--	33	0
Large granulomas	*Diameter > 200 µm*		*Diameter > 400 µm*		*Area > 0.05 mm^2*	
	90	5	51	0	67	8
Submucosal granulomas	45	5	39	6	44	12
Ulcers lined by bands of epithelioid histiocytes	45	5	61	0	61	8
Disproportionate submucosal inflammation	65	5	--	--	67	10
Architectural distortion distant to granulomatous inflammation	--	--	0	62	--	--

On the other hand, studies from Western China did not find histology useful

in distinguishing ITB and CD, but only assessed a few parameters including ulceration, lymphoid aggregates, chronic inflammation, confluent granulomas and caseating granulomas.[37] The importance of taking multiple biopsies in cases of suspected ITB has been emphasized and significantly increases the diagnostic yield.[39] Biopsies should be taken from all segments of the bowel including both endoscopically normal and abnormal areas.[39] In particular, ulcerated areas should be thoroughly sampled (including multiple biopsies from both the base and the edge of the ulcer) as the diagnostic yield in ITB is highest in these lesions.[38]

Several studies suggest a role for PCR for mycobacterial DNA in the differential diagnosis of ITB and CD.[34,38] Four retrospective studies on formalin-fixed, paraffin embedded colonoscopic biopsy specimens reported positive results in 22% (13/60), 45% (18/40), 64% (25/39), 75% (27/36) of ITB patients.

Radiology:

Barium studies allow visualization of the mucosal surface and luminal diameter and are valuable in demonstrating the inflammatory and cicatrising lesions found in both ITB and CD. Earlier work focussed on the pattern of ileo-caecal involvement as a means of diagnosing ITB (Fig 5). Examples of these include the Fleischner sign (a thickened patulous ICV combined with a narrowed terminal ileum) and Stierlin's sign (a rapid

emptying of contrast through a gaping ileo-ceacal valve into a shrunken or 'amputated' caecum)[42].

A long segment of terminal ileal involvement, with skip lesions and preservation of the valve and caecum was considered typical of CD (Fig 6). However, these radiological signs are non-specific for either ITB or CD and a variety of other lesions such as ulcers, strictures, fistulas, fold thickening, mucosal nodules and bowel loop separation have been described in both conditions.[43]

With contrast enhanced CT scanning and MRI, and abdominal ultrasound bowel wall changes, mesenteric attachments, lymph nodes and other abdominal organs can be assessed and this may be useful in differentiating CD from ITB. When ITB occurs with concurrent TB of the peritoneum, mesentry and abdominal lymph nodes cross sectional imaging is often diagnostic in the high-prevalence environment. (Table 3).

However, in isolated ileo-caecal TB cross sectional imaging is not diagnostic. ITB findings in this region include asymmetric caecal wall thickening,[44] an inflammatory mass centred around the caecum and enveloping the terminal ileum and small homogenous pericaecal lymph nodes.[45] Features of CD include symmetrical bowel wall thickening, fibrofatty proliferation of the mesentry known as 'creeping fat', regional mesenteric nodes measuring 3-8 mm and enlarged mesenteric vascular bundles in the

involved mesentry known as the comb sign.[46, 47] Extra-intestinal features of CD such as fatty liver, gallstones, primary sclerosing cholangitis and sacro-ileitis may also be seen on CT scan and MRI.[46, 48]

Radiological imaging of the abdomen is invaluable in determining the extent of intestinal disease in both CD and ITB. The presence of extra-luminal features may favour either ITB or CD. Functional MRI with improved luminal contrast techniques and CT enteroclysis allow better fistula definition and distinction between bowel wall fibrosis and inflammation;[49] however, the diagnostic capabilities of these new imaging modalities in environments with high rates for TB is unknown. At present conventional radiology in the majority of cases is not diagnostic.

Table 3. Radiological Features of ITB with Abdominal Involvement

Abdominal nodes
12-50 mm
Mesenteric, peri-pancreatic, periportal, pericaval, upper para-aortic
Central areas of low attenuation
Peripheral rim enhancement
Node calcification
Ascites
Free
Fibrin stranding

Loculated
Mesentry
Thickening
Nodularity
Abscesses
'Caked' omentum
Portal vein thrombosis
Hepato-splenic lesions
Tuberculoma
Diffuse micro-abscesses
Bowel wall thickening

Laparoscopy:

No systematic laparoscopic study comparing ITB to CD has been conducted. Laparoscopy has been used as a diagnostic test in CD and the presence of creeping fat is associated with transmural inflammation.[50] However, mesenteric fat wrapping has also been described in patients undergoing laparotomy for tuberculosis in India.[21, 26] Laparoscopy can be used for the diagnosis of peritoneal tuberculosis but its role in ITB is less clear.[51]

Management of Crohn's Patients in Regions with High Rates for Tuberculosis:

Managing CD with steroids, immunomodulatory therapy and biologicals in TB endemic regions presents unique challenges. International guidelines have evolved largely from research in populations with low TB prevalence and may not be appropriate in this environment. Therapies targeting TNF-α are associated with a higher incidence of TB than expected, and with extra-pulmonary and disseminated infection. This appears to be a class effect not unique to Infliximab. As such it is widely recommended that all patients be screened for active and latent TB before initiating any anti-TNF-α treatment. [52] However, protocols for screening may not be adequate in endemic areas and a high index of suspicion is paramount. A detailed history of past infection, BCG vaccination, duration and adequacy of past treatment, recent contacts and suggestive symptoms must be ascertained. Furthermore, in this setting a chest radiograph is mandatory. If indicative every attempt must be made to exclude active infection, including sputum analysis and bronchoscopy as appropriate.

Far less clear is the most appropriate way in which to screen the asymptomatic patient (with a normal chest radiograph) for latent TB, particularly in areas with extensive BCG vaccination. Tuberculin Skin Test (TST) has several limitations; interpretation is subject to observer bias, requires a second visit to read the results and sensitivity can be reduced in immunocompromised individuals.[53] Particularly controversial in the setting of endemic tuberculosis is what cut-off constitutes a positive TST as the test is hampered by cross-reactivity of PPD antigens also present in the

Mycobacterium bovis strain used for BCG vaccination and in non-tuberculous mycobacteria (NTM). As such there is a possibility of false-positive testing, which appears to diminish 15-years-postvaccination.[54]

The traditional cut-off used in populations with widespread BCG vaccination is 10 mm; increasing this to 15 mm appears to improve specificity in immunocompetent individuals, but at the expense of test sensitivity. [54] However, patients with CD have a very high incidence of anergy to TST and in keeping with international guidelines most considered appropriate for anti-TNF-α therapy will be receiving concurrent immunosuppressive medication or corticosteroids. [52]

In general, a negative TST does not exclude latent TB in patients with CD receiving immunosuppressive therapy. However, a positive TST would aid in the decision to implement TB prophylaxis, particularly if BCG vaccination was more than 15 years previously.

It would be prudent to err on the side of caution and use a cut-off of >5 mm to recommend TB prophylaxis in immunosuppressed patients with CD living in TB endemic areas. This, however, remains to be validated.

In an attempt to circumvent the problems of TST, newer IFN-γ based assays have been developed to evaluate latent TB. These tests use antigens specific to *M.*

tuberculosis, in particular those in the region of difference 1; early secreted antigenic target-6 and culture filtrate protein 10. These novel assays determine the magnitude of interferon gamma release by T-cells on exposure to these antigens *in vitro.* Two enzyme linked immunoassay tests are currently available; QuantiFERON-TB Gold and QuantiFERON-TB Gold in-tube (Cellestis, Carnegie, Australia). In low risk populations these assays appear at least comparable with TST in detecting active and latent TB, with superior specificity. There are, however, valid concerns regarding sensitivity of these assays in areas of high-TB prevalence and in the immunocompromised host, and as such further studies are required before meaningful recommendations can be formulated.

A third IFN-γ based test, the T-SPOT.*TB* (Oxford Immunotec, Oxford, UK) may prove better in this setting. This enzyme linked immunospot assay is more specific than TST in BCG vaccinated individuals, is less likely to be false negative in the setting of HIV infection and less likely to produce indeterminate results when compared with QuantiFERON-gold.

One possible way in which to improve the accurate diagnosis of latent TB using these tests is to perform TST and subsequently retest all positives using an interferon based investigation assay. Currently none of the IFN-γ based assays can reliably distinguish active from latent TB, nor predict which patients with latent TB will develop active infection.

Tuberculosis Prophylaxis in Patients Deemed Appropriate for Anti-TNF-α Therapy:

Patients with a positive TST (but normal chest radiograph), a history of inadequately treated TB in the past or those with an abnormal chest radiograph consistent with past TB should commence treatment for latent tuberculosis before receiving anti-TNF-α agents. [55] It must, however, be noted that while reducing the risk of progression to active TB this is not 100% effective and as such all patients must be assessed regularly for evidence of reactivation.[56]

The choice of drug regimen and duration of therapy currently remains unclear and recommendations vary. There are several possibilities: isoniazid for 6-12 months, rifampicin for 4 months or rifampicin plus isoniazid for 3 months. Short course therapy with rifampicin and pyrazinamide should be avoided due to unacceptable risk of hepatotoxicity.[57] In high-burden TB areas with increasing emergence of multi-drug resistant TB, rifampicin monotherapy would not be considered appropriate. Isoniazid monotherapy is effective and widely used, but carries the potential of drug resistance. The appropriate duration of therapy before commencing anti-TNFs has not been established but most recommendations suggest completion of at least 2 months.[55]

Treatment of Active Tuberculosis Prior to Initiating Anti-TNF-α Therapy:

Active, untreated pulmonary or extra-pulmonary TB is an absolute

contraindication to the use of anti-TNF-α therapy.[52] These patients should ideally receive full anti-tuberculosis therapy before initiation of anti-TNF-α treatment.[55] However, it may be acceptable to start therapy after completion of at least 2 months of full TB treatment. [58] This approach is somewhat risky, requires vigilant monitoring and should only be considered in severe cases of CD where benefit is thought to outweigh risk.

Treatment of Active Tuberculosis in Patients Receiving Anti-TNF-α Therapy:

Patients who develop active TB whilst receiving anti-TNF-α therapy should receive full anti-tuberculous therapy. It has been suggested that anti-TNF-α therapy can be continued concurrently if clinically indicated, when the risks of a flare of CD are considered high. [58]

Risks of Tuberculosis with Other Immunosuppressant Therapies for Crohn's Disease:

Patients with Crohn's disease are frequently exposed to other immunosuppressives; in particular corticosteroids, azathioprine and 6-mercaptopurine. These are also associated with an increased risk of *M. tuberculosis* reactivation. There is, however, no clear guideline on TB prophylaxis with these agents in CD. Most recommendations are published in the rheumatology, respiratory and transplant literature and while prophylaxis reduces the risk of developing active TB in this setting, the use of

TST carries the same limitations as those described above.[59] In our area of endemic TB, we routinely perform chest radiography on all IBD patients before initiating any form of immunosuppression and maintain a low threshold to repeat this investigation should the clinical suspicion arise. INH prophylaxis is considered in patients with radiological abnormalities suggesting previous TB, in whom active disease has been excluded.

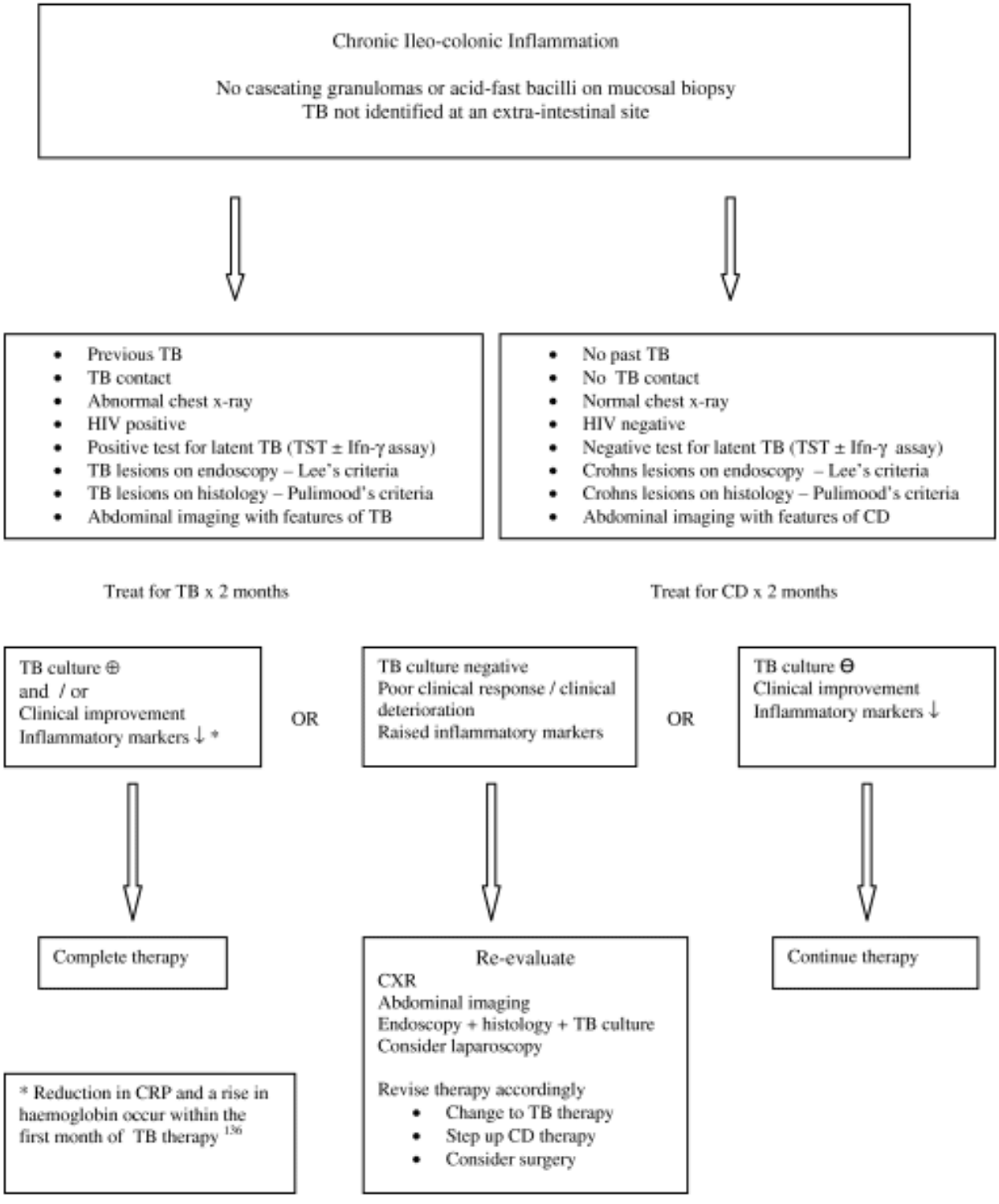
Future perspectives:

Tuberculosis remains an overwhelming health problem in the developing world but migration and the emergence of new drug resistant strains has global public health implications. Gastroenterologists throughout the world, particularly those in developing countries or those serving immigrant communities must include ITB in the differential diagnosis of CD. Intestinal tuberculosis must be actively excluded after careful clinical, radiological and endoscopic evaluation. Culture for *M. tuberculosis* on endoscopic mucosal biopsy specimens is mandatory in all patients; however, the value of systematic histological assessment looking for features of ITB must not be underestimated.

In patients with confirmed CD the approaches to screening for latent tuberculosis remain controversial. Further evaluation of the screening tests, particularly in the developing world, is required. After initiating treatment with steroids,

immunomodulatory or biological therapy vigilance for reactivation of latent tuberculosis must be sustained. Further research in the diagnosis of tuberculosis, and application of recent developments in the genetic and serological diagnosis of IBD, will certainly play a future role in the diagnosis and management of CD in regions with high rates of tuberculosis.

The following diagnostic and therapeutic algorithm is suggested by Epstein et al, [22] based on the available evidence and their experience, for cases where diagnostic uncertainity exists.


Chronic Ileo-colonic Inflammation
No caseating granulomas or acid-fast bacilli on mucosal biopsy
TB not identified at an extra-intestinal site
Previous TB
TB contact
Abnormal chest x-ray
HIV positive
Positive test for latent TB (TST ± Ifn-γ assay)
TB lesions on endoscopy – Lee's criteria
TB lesions on histology – Pulimood's criteria
Abdominal imaging with features of TB
No past TB
No TB contact
Normal chest x-ray
HIV negative
Negative test for latent TB (TST ± Ifn-γ assay)
Crohns lesions on endoscopy – Lee's criteria
Crohns lesions on histology – Pulimood's criteria
Abdominal imaging with features of CD
Treat for TB x 2 months
Treat for CD x 2 months
TB culture ⊕
and / or
Clinical improvement
Inflammatory markers ↓ *
OR
TB culture negative
Poor clinical response / clinical deterioration
Raised inflammatory markers
OR
TB culture ⊖
Clinical improvement
Inflammatory markers ↓
Complete therapy
Re-evaluate
CXR
Abdominal imaging
Endoscopy + histology + TB culture
Consider laparoscopy
Revise therapy accordingly
Change to TB therapy
Step up CD therapy
Consider surgery
Continue therapy
* Reduction in CRP and a rise in haemoglobin occur within the first month of TB therapy [136]

MATERIALS AND METHODS

Study methods:

A prospective study was undertaken in the Department of Gastroenterology at Stanley Medical College, Chennai, a tertiary referral center in Tamil Nadu state, between January 2006 and December 2007.

Inclusion criteria:

Symptomatic patients presenting with abdominal pain, chronic mucoid diarrhea, fever, weight loss, altered bowel habits and features of malabsorption, past history of tuberculosis (TB) with or without treatment, belonging to either sex, age range between 15 and 60yrs, with colonoscopic findings suggestive of ileocaecal or colonic tuberculosis (C-TB), Crohn's disease (C-CD) or undefined disease (C-UD) were included. The clinical details, laboratory investigations, colonoscopic findings and histology were noted on a pre-structured proforma (Annexure I). Treatment and follow up were not included as part of study.

Exclusion criteria:

Patients at extremes of age (<14yrs, ≥61yrs), known case of ileocecal/colonic tuberculosis or Crohn's disease on treatment and follow-up, ischemic bowel disease,

radiation induced injury and diverticular disease of the colon were excluded.

Ethics committee approval:

Ethics committee approval of the Institution was obtained prior to the initiation of the study.

***Investigations*:**

All patients had a baseline hematological and biochemical evaluation. These included

- Complete hemogram: hemoglobin and packed cell volume, total and differential leucocyte counts and erythrocyte sedimentation rate
- Blood biochemistry: Blood sugar, blood urea, serum creatinine and serum electrolytes
- Serum C-Reactive protein (CRP)
- Serum protein and albumin
- Urine analysis
- Motion examination
- Mantoux test
- X-ray chest

Colonoscopy:

All patients were prepared for colonoscopy using Polyethylene Glycol (PEG) with

electrolyte solution. Patients were instructed to consume clear liquids for 24 hrs prior to the procedure, along with the PEG solution dissolved in 2 liters of tap water, which had to be consumed the previous evening between 6 and 8 pm. Colonoscopy was performed using a videoendoscope, Olympus – SMARTAGE 140 SERIES (Manufacturer: OLYMPUS Corporation, Japan).

After a perianal examination, the entire colon was screened for mucosal lesions. Ileal intubation was attempted in all the cases and tissue was taken for histopathology.

A diagnosis of ileocaecal/colonic TB (Gp I: C-TB) was considered when at least 3 of the 6 under mentioned characteristics were noted. Findings included:

- Isolated ileal or ileocecal involvement
- Destruction of ileocecal valve
- Circumferential ulcers
- Short segment strictures
- Mucosal nodularity
- Pseudopolyps

A diagnosis of ileo caecal/colonic CD (Gp II: C-CD) was based on the presence of combination of 4 or more under mentioned criteria.

- Perianal lesions
- Aphthous ulcers or serpiginous, stellate, fissuring and deep ulcers of varying sizes with normal intervening mucosa
- Ileal involvement with preservation of ileocecal valve

- Skip lesions
- Long segment strictures
- Cobblestoning of the mucosa

Colonoscopic findings were considered as undefined (Gp III: C-UD) when there was an overlap of 4 or more findings of C-TB and C-CD.

Histopathological analysis:

Multiple biopsy specimens for histology were taken both from the diseased and normal appearing mucosa, the latter at 10 cm interval from ileum to rectum. The pathologist was blinded to the colonoscopic findings. Serial tissue sections of biopsy samples were cut from paraffin blocks into 4-5mm thickness. They were then stained with hematoxylin and eosin and studied under light microscope (low and high power).

The histological findings for TB (Gp A: H-TB) were largely based on the characteristics of the granuloma including,

- Large (>200μm) granulomas, caseating, confluent and multiple
- Submucosal inflammation
- Epithelioid cells

The histological diagnosis of CD (Gp B: H-CD) was considered when the following findings were present.

- Small (<100μm) granulomas, non-caseating and solitary
- Transmural chronic inflammatory cell response

- Glandular distortion distant from the site of granulomatous inflammation
- Presence of a granulomatous response in normal appearing mucosa

When the histological report was equivocal i.e. an overlap of findings of H-TB and H-CD, these were reported as inconclusive (Gp C: H-IC).

Non-specific colitis (Gp D: H-NSC) was defined when there were non-specific changes of chronic inflammatory response with no significant mucosal distortion.

The histological diagnosis was considered as the gold standard and this was correlated with the colonoscopic diagnosis and the individual variables were statistically analyzed for significance.

Statistical analysis:

The variables were analyzed with student's t-test and Chi-square test for statistical significance. P value of < 0.05 was considered statistically significant. Univariate and multivariate analysis was performed to find out the combinations of colonoscopic variables that could independently predict the presence of the disease.

RESULTS AND ANALYSIS

Demographic and clinical profile:

Eighty-two patients presented with clinical symptoms and signs of ileocecal/colonic tuberculosis or Crohn's disease during the study period. 58 individuals fulfilled the inclusion criteria for C-TB, C-CD and C-UD. Overall there were 33 males and 25 females. TB was prevalent among the patients from lower socio-economic strata, whereas CD was commoner among the affluent. Clinically, the prevalence of TB was equal between both genders; symptoms of fever, blood and mucous diarrhoea and abdominal mass dominated. In CD, the disease was more common amongst women; perianal symptoms, periumbilical abdominal pain, anemia and hypoproteinemia, predominated in these patients. Treatment for TB was seen equally in both groups. Three (5.2%) patients had a family history of TB. None had a family history of inflammatory bowel disease. Table 1 summarizes the demographic and clinical profile

of patients with TB and CD.

Table 1: Demographic and clinical profile of TB and CD.

Variables	**Clinical TB (n=36) (%)**	**Clinical CD (n=22) (%)**
Mean age (yrs)	33 ± 18.6	27 ± 5.2
M:F	25:11	8:14
Mean per capita income (Rs)	815	1440
Smokers	7 (19.4)	2 (9.1)
Alcoholics	8 (22.2)	4 (18.2)
Tobacco chewers	3 (8.3)	1 (4.6)
H/O appendectomy	2 (5.6)	1 (4.6)
H/O surgery for pile/fissure/perianal abscess	3 (8.3)	2 (9.1)
Treatment for tuberculosis	3 (8.3)	2 (9.1)
Mean duration of illness (months)	13	11
Interval between onset and diagnosis (months)	14	13.5
Fever	15 (41.6)	7 (31.8)
Abdominal pain	8 (22.2)	19 (86.4)
Diarrhoea	11 (30.6)	5 (22.7)
Blood and mucus	19 (52.7)	12 (54.5)
Mass abdomen	23 (63.8)	11 (50)
Perianal symptoms (fissure, hemorrhoid, abscess)	3 (8.3)	7 (31.8)
Oedema legs	5 (13.8)	6 (27.2)
Extra intestinal manifestations	None	None
Anemia	4 (11.1)	7 (31.8)
Hypoproteinemia	3 (8.3)	6 (27.2)

Colonoscopic diagnosis:

Among the 58 cases who underwent colonocscopy, 32 (55.1%) patients had

features favoring TB (C-TB), 11 (11.9%) had features of CD (C-CD) and in 15 (25.9%) a diagnosis was not possible (C-UD) (vide criteria mentioned above). (Table 2) (Fig 7).

Table 2: Colonoscopic diagnosis

Groups	Diagnosis	No. of cases (%)
I	Tuberculosis	32 (55.1)
II	Crohn's disease	11 (18.9)
III	Undefined disease	15 (25.9)

The colonoscopic findings in the various groups are shown in Table 3a and their statistical significance in 3b (Fig 8).

Table 3a: Colonoscopic findings in all the three groups

Colonoscopic findings	C-TB (n=32) (%)	C-CD (n=11) (%)	C-UD (n=25) (%)
Isolated ileal disease	4 (15.5)	5 (45.5)	4 (26.6)
Ileo-cecal involvement	7 (21.8)	1 (9.1)	3 (20)
Ileocecal valve destruction	4 (12.5)	1 (9.1)	2 (13.3)
Short segment strictures	3 (9.4)	1 (9.1)	1 (6.7)
Circumferential ulcers	7 (21.8)	None	2 (13.3)
Mucosal nodularity	13 (40.6)	2 (18.1)	5 (33.3)
Pseudopolyps	None	1 (9.1)	2 (13.3)
Perianal lesions	2 (6.3)	4 (36.4)	3 (20)
Aphthous ulcers	2 (6.3)	8 (72.7)	2 (13.3)
Skip lesions	1 (3.1)	2 (18.1)	None
Long segment strictures	None	3 (27.3)	2 (13.3)
Cobblestoning	1 (3.1)	4 (36.4	2 (13.3)

Table 3b: Significance of colonoscopic findings in C-TB and C-CD

Colonoscopic findings	C-TB (n=32) (%)	C-CD (n=11) (%)	P value
Isolated ileal disease	**4 (15.5)**	**5 (45.5)**	**0.02**
Ileo-cecal involvement	7 (21.8)	1 (9.1)	0.34
Ileocecal valve destruction	4 (12.5)	1 (9.1)	0.76
Short segment strictures	3 (9.4)	1 (9.1)	0.97
Circumferential ulcers	7 (21.8)	None	0.09
Mucosal nodularity	13 (40.6)	2 (18.1)	0.17
Pseudopolyps	None	1 (9.1)	0.08
Perianal lesions	**2 (6.3)**	**4 (36.4)**	**0.01**
Aphthous ulcers	**2 (6.3)**	**8 (72.7)**	**0.001**
Skip lesions	1 (3.1)	2 (18.1)	0.06
Long segment strictures	**None**	**3 (27.3)**	**0.002**
Cobblestoning	**1 (3.1)**	**4 (36.4)**	**0.003**

The colonoscopic findings of isolated ileal involvement, aphthous ulcer, cobble stoning, long segment strictures, and perianal involvement favored a diagnosis of Crohn's disease compared to their prediction of intestinal tuberculosis ($P<0.05$) (Table 3b). None of the findings were typical for TB. Circumferential ulcers and mucosal nodularity were more common in C-TB, though it did not reach statistical significance.

Histological interpretation:

Nine (15.5%) and 16 (27.6%) patients had histological confirmation of TB (H-TB) and CD (H-CD) respectively. The histology was inconclusive (H-IC) or non-specific (H-NS) in 18 (31%) and 25 (25.9%) respectively. Thus histopathology

confirmation was possible in less than 50% for both CD and TB (Table 4) (Fig 9).

Table 4: Histological diagnosis

Colonoscopy correlated with histology in 6 patients each with C-TB (18.8%) and C-CD (54.5%) (Table 5). However in 5 patients (15.6%) with colonoscopic TB (C-TB) the histology was that of CD (H-CD) and in one patient (9%) with colonoscopic CD (C-CD), the histology was that of TB (Fig 10, 11, 12).

Table 5: Colonoscopic diagnosis compared with histological diagnosis

The colonoscopic findings in various groups based on the histological diagnosis are shown in Table 6a and their statistical significance in Table 6b (Fig 13).

Table 6a: Colonoscopic findings in various groups based on histological diagnosis

Findings	H-TB (n=9) (%)	H-CD (n=16) (%)	H-IC (n=18) (%)	H-NS (n=15) (%)
Isolated ileal disease	2 (22.2)	6 (37.5)	3 (16.7)	2 (13.3)
Ileo-cecal involvement	4 (44.4)	2 (12.5)	3 (16.7)	2 (13.3)
Ileocecal valve destruction	3 (33.3)	1 (6.3)	2 (11.1)	1 (6.7)
Short segment strictures	2 (22.2)	2 (12.5)	1 (5.6)	None
Circumferential ulcers	4 (44.4)	2 (12.5)	1 (5.6)	2 (13.3)
Mucosal nodularity	5 (55.5)	4 (25)	6 (33.3)	5 (33.3)
Pseudopolyps	None	2 (12.5)	1 (5.6)	None
Perianal lesions	1 (11.1)	4 (25)	3 (16.7)	1 (6.7)
Aphthous ulcers	2 (22.2)	8 (50)	1 (5.6)	1 (6.7)
Skip lesions	None	1 (6.3)	1 (5.6)	1 (6.7)
Long segment strictures	1 (11.1)	3 (18.8)	1 (5.6)	1 (6.7)
Cobblestoning	1 (11.1)	3 (18.8)	3 (16.7)	None

Table 6b: Comparison of the colonoscopic findings with H-TB and H-CD

Findings	H-TB (n=9) (%)	H-CD (n=16) (%)	P value
Isolated ileal disease	2 (22.2)	6 (37.5)	0.73
Ileo-cecal involvement	4 (44.4)	2 (12.5)	0.19
Ileocecal valve destruction	3 (33.3)	1 (6.3)	0.22
Short segment strictures	2 (22.2)	2 (12.5)	0.95
Circumferential ulcers	4 (44.4)	2 (12.5)	0.19
Mucosal nodularity	5 (55.5)	4 (25)	0.27
Pseudopolyps	None	2 (12.5)	0.74
Perianal lesions	1 (11.1)	4 (25)	0.75
Aphthous ulcers	2 (22.2)	8 (50)	0.35
Skip lesions	None	1 (6.3)	0.80
Long segment strictures	1 (11.1)	3 (18.8)	0.95
Cobblestoning	1 (11.1)	3 (18.8)	0.95

When individual colonoscopic findings were correlated with histology, none of the parameters predicted the histological diagnosis of TB or CD. On multivariate

analysis, mucosal nodularity alone predicted TB, and aphthous ulcers with isolated ileal involvement predicted CD.

The accuracy of colonoscopy in diagnosing C-TB among the histopathologically proven cases is only 50% with a sensitivity of 66% and a specificity of 47%. Whereas, the accuracy, sensitivity and specificity were 84%, 37.5% and 84% respectively, when colonoscopy was used in the diagnosis of histopathologically proven cases of Crohn's disease. This showed the comparatively better role of colonoscopy in the diagnosis of suspected cases of Crohn's disease, than in the prediction of ileocecal tuberculosis.

In the patients in C-UD group (15 patients), in whom colonoscopy could not distinguish CD or TB, 7 (46.6%) had significant histological features; two (13.3%) patients had a histological diagnosis of TB (H-TB) and 5 (33.3%) had histological features of CD (H-CD). Table 7 highlights the colonoscopic features in these 7 cases (Fig 14).

Table 7. Colonoscopic findings in C-UD group, with significant histology.

Colonoscopic Findings	**H-TB (n=2) (%)**	**H-CD (n=5) (%)**	**P value**
Isolated ileal disease	None	1 (20)	0.25
Ileo-cecal involvement	2 (100)	3 (60)	0.09
Ileocecal valve destruction	2 (100)	2 (40)	0.07
Short segment strictures	None	1 (20)	0.25
Circumferential ulcers	1 (50)	2 (40)	0.30

Mucosal nodularity	1 (50)	2 (40)	0.30
Pseudopolyps	None	1 (20)	0.25
Perianal lesions	1 (50)	2 (40)	0.30
Aphthous ulcers	1 (50)	2 (40)	0.30
Skip lesions	None	1 (20)	0.25
Long segment strictures	1 (50)	2 (40)	0.30
Cobblestoning	None	None	NA

When the colonosocpic features were reanalyzed appropriating those positive on histology i.e combining patients with colonoscopic TB or CD (C-TB and C-CD) and those with significant histology in C-UD group (H-TB and H-CD), it was seen that addition of these cases did not change the significance of findings distinguishing CD from TB at colonoscopy (Table 8). However, in addition to other significant parameters described before (Table 3b), skip lesions also predicted the diagnosis of CD.

Table 8. Statistical analysis after combining patients with significant histology in C-UD group with C-TB and C-CD

Colonoscopic Findings	**H-TB (n=34) (%)**	**H-CD (n=16) (%)**	**P value**
Isolated ileal disease	**4 (11.7)**	**6 (37.5)**	**0.01**
Ileo-cecal involvement	9 (26.4)	4 (25)	0.96
Ileocecal valve destruction	6 (17.6)	3 (18.8)	0.95
Short segment strictures	3 (8.8)	2 (12.5)	0.75
Circumferential ulcers	8 (23.5)	2 (12.5)	0.09
Mucosal nodularity	14 (41.2)	4 (25)	0.08
Pseudopolyps	0	2 (12.5)	0.08

Perianal lesions	**3 (8.8)**	**6 (37.5)**	**0.01**
Aphthous ulcers	**3 (8.8)**	**10 (62.5)**	**0.001**
Skip lesions	**1 (2.9)**	**3 (18.8)**	**0.05**
Long segment strictures	**1 (2.9)**	**5 (31.3)**	**0.003**
Cobblestoning	**1 (2.9)**	**4 (25)**	**0.002**

DISCUSSION

Recent years have shown an increase in the prevalence of inflammatory bowel disease and tuberculosis. The distinction between intestinal tuberculosis and Crohn's disease is important since both can present with overlapping clinical, colonoscopic and histological features. In the West, TB is considered in the differential diagnosis of all suspected cases of CD, particularly among Asian migrants. [60] Management of these conditions needs exclusion of the other, because of the detrimental effects of

immunosuppression and drug toxicities.

Totally 58 patients met with the inclusion criteria. Majority of the patients with a clinical suspicion of TB were from were from the lower socio-economic group, whereas patients with clinical CD were from upper socio-economic background. The mean age of presentation was 32 yrs for TB and 27 yrs for CD, which is a well-established fact observed in the literature.

Five patients were exposed to tuberculosis infection in the past, of whom two developed Crohn's diseases. This could be explained by the possible causal role of atypical mycobacteria or the possible flaw in the histological interpretation of granulomas and submucosal lymphoid which could also be seen in intestinal tuberculosis.

During colonoscopy, ITB was suspected in 55% of cases, and CD in 11%, based on the criteria established by Lee et al. [37] The remaining patients had overlapping findings suggesting an undefined disease. According to these criteria, the colonoscopic appearance of transverse ulcers, pseudopolyps, and a patulous ileo-caecal valve predicted a diagnosis of intestinal tuberculosis and that of anorectal lesions, longitudinal ulcers, apthous ulcers, cobblestone appearance predicted a diagnosis of Crohn's disease, which has a positive predictive value of for 88.9% ITB and 94.9% for CD.

Among the patients with a colonoscopic diagnosis of ITB, mucosal nodularity was commonly seen in the majority, followed by ulceronodular growth and linear ulcers. In a similar study by Sato et al, the colonoscopic mucosal appearance was classified into 4

types; one among them is the circumferential ulceration with nodularity, which was seen in 36%. [61]

In patients with a colonoscopic diagnosis of Crohn's disease, aphthous ulcer was the predominant finding in nearly three fourths, followed by isolated ileal involvement. Jeong et al in a similar study on terminal ileoscopy in patients with Crohn's disease, observed ulcers or erosions in two thirds, however there is no description on the morphological appearance of ulcers. [62] In the current study, apart from the presence of aphthous ulcers, patients with a colonoscopic diagnosis did not have any other morphological types of ulcers (like circumferential or linear ulcers). However, this could not be projected as statistically significant, due to the very small size.

On correlating colonoscopic findings in both the conditions, the presence of aphthous ulcer, isolated ileal involvement, cobblestoning, long segment strictures and perianal involvement predicted the diagnosis of CD than ITB, with variable significances.

This was similar to the observations by Lee et al. [37] However, in the current study, the diagnosis of ITB could not be established solely on colonoscopic basis. This could be due to the observer variability.

The histolological criteria for diagnosis of ITB and CD were based on the observations by Pulimood et al. [40] In their study, they have found that the presence of multiple (>5), large (>193μm), confluent granulomas with caseating necrosis favoured ITB, whereas the presence of infrequent, small (<95 μm) granulomas, microgranulomas

(poorly organized collections of epithelial histiocytes), focally enhanced colitis and chronic inflammation even in normal appearing mucosa favoured CD. The same criteria were applied in the histological diagnosis of the current study.

When the colonoscopic findings were correlated with histological diagnosis, mucosal nodularity, circumferential ulcers, ulceronodular growth and combined ileocecal involvement were seen in around half of the cases of ITB and aphthous ulcer and isolated ileal involvement were seen in half of CD patients. However, this could not be shown statistically significant as due to the small sample size.

The colonoscopic and histological correlation was possible in only 18.8% of ITB and 54.5% of CD. This is similar to study by Jeong et al, where the histological positivity was possible in < 10% of the cases who had macroscopic abnormalities in the terminal ileum. [62]

Colonoscopy was only 50% accurate with 66% sensitivity and 47% specificity in the diagnosis of intestinal tuberculosis, whereas it was 84% accurate with 37.5% sensitivity and 84% sensitivity in the diagnosis of Crohn’s disease. In their study, Lee et al has shown that, the diagnosis of either intestinal tuberculosis or Crohn's disease would have been made correctly in 77 of their 88 patients (87.5 %), incorrectly in seven patients (8.0 %), and would not have been made in four patients (4.5 %), an observation similar to that in the present study. [37]

There is a group of patients who had indeterminate findings in colonoscopy (25%) and inconclusive histology (31%). Among those with indeterminate colonoscopic

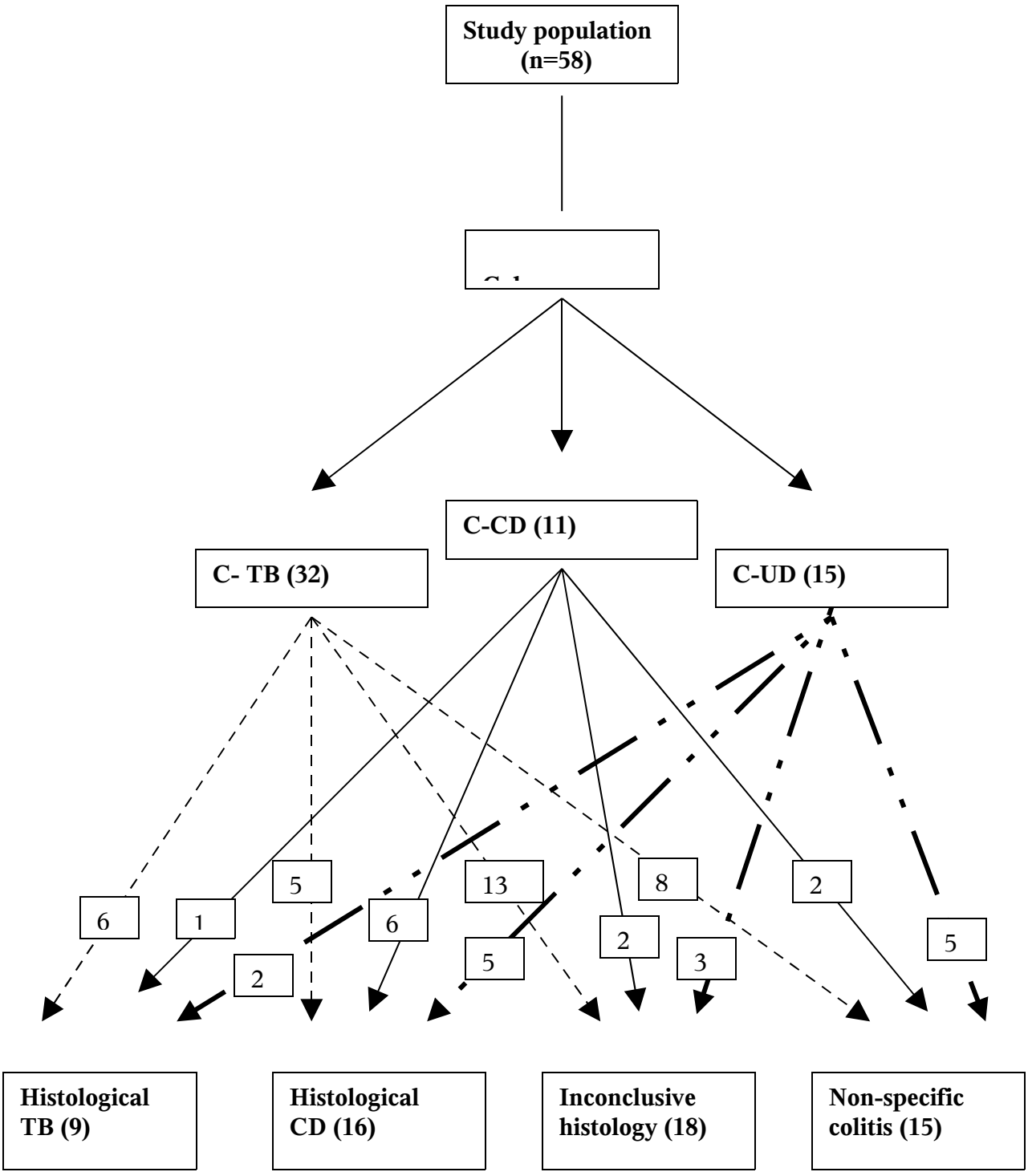
findings, one third had histological features suggestive of CD. This explains the variable presentation of Crohn's disease, which had overlapping findings in colonoscopy.

SUMMARY AND CONCLUSIONS

Summary:

- Study population consisted of 58 cases.
- Mean age was 30 ± 12.44 yrs (range: 18 – 48yrs) with M: F ratio of 1.3:1.
- Patients with a clinical suspicion of TB were from lower socio-economic strata, whereas those with CD were from affluent society.
- Colonoscopic diagnosis of intestinal tuberculosis was in 55.1%, Crohn's disease in 18.9%, and indeterminate disease in 25.9% of cases.
- Colonoscopic findings of isolated ileal involvement, aphthous ulcer, cobble stoning, long segment strictures, and perianal involvement favored a diagnosis of Crohn's disease rather than intestinal TB ($P<0.05$).
- Histopathology confirmed intestinal tuberculosis in 15.5% of patients, Crohn's disease in 27.6%, inconclusive histology in 31% and nonspecific colitis in 25.9%.
- Colonoscopic diagnosis correlated with histological diagnosis in 18.8% patients with intestinal tuberculosis and 54.5% with Crohn's disease.
- Colonoscopic findings were statistically insignificant when they were correlated with the histological diagnosis.
- Colonoscopy was only 50% accurate with 66% sensitivity and 47% specificity in the diagnosis of intestinal tuberculosis, whereas it was 84% accurate with 37.5% sensitivity and 84% sensitivity in the diagnosis of Crohn's disease.

- Individual findings did not signify the colonoscopic prediction of these diseases.
- Multivariate analysis showed the presence of mucosal nodularity predicted intestinal tuberculosis, and aphthous ulcers with isolated ileal involvement predicted Crohn's disease.
- On appropriating those positive on histology in undefined group with colonoscopic TB or CD, in addition to other significant parameters, skip lesions also predicted the diagnosis of CD.


Study population (n=58)
C-CD (11)
C- TB (32)
C-UD (15)
6
1
5
2
6
13
5
8
2
3
2
5
Histological TB (9)
Histological CD (16)
Inconclusive histology (18)
Non-specific colitis (15)

Conclusions:

- This study has looked into the role of colonoscopy in predicting the diagnosis of ileocecal tuberculosis and Crohn's disease.
- Colonoscopic findings of isolated ileal involvement, aphthous ulcer, cobblestoning, long segment strictures, skip lesions and perianal involvement favors a diagnosis of Crohn's disease than that of intestinal tuberculosis.
- Correlation of colonsocopy with histology is poor for both CD and TB.
- The accuracy, sensitivity and specificity of colonoscopy was better and superior in the diagnosis of Crohn's disease, than in the diagnosis of TB.
- Large-volume case-control studies may be necessary to further validate the present information in a country like ours where CD and TB are close mimickers with similar clinical presentation, colonoscopy features and the overlap in histology between the two diseases.

BIBLIOGRAPHY

1. http://www.who.int.tb.publications/2007/factsheet_2007.pdf. Last accessed 18 April 2007.
2. Global Tuberculosis Control Report WHO 2007: Key findings. http://www.int/tb/publications/global_report/2007/key_findings/en/index.html. Last accessed 18 April 2007.
3. Toms I, Bitalo L. Cape Town TB control. A partnership between the Provincial Administration of the Western Cape Metropole Region and the City of Cape Town. Progress Report 1997-2003. http://www.hst.org.za/publications/618. Last accessed 18 April 2007.
4. Edginton ME, Wong ML, Phofa R, *et al.* Tuberculosis at Chris Hani Baragwanath Hospital: numbers of patients diagnosed and outcomes of referrals to district clinics. Int J Tuberc Lung Dis 2005; 9: 398-402.
5. Raviglione MC, Smith IM. XDR Tuberculosis - Implications for global public health. NEJM 2007; 356: 656-9.
6. Gandhi NR, Moll A, Sturm AW, *et al.* Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006; 368: 1575-80.
7. Pettengell KE, Larsen C, Garb M, *et al.* Gastrointestinal tuberculosis in patients with pulmonary tuberculosis. Q J Med 1990; 74: 303-8.
8. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res 2004; 120: 305-15.
9. Ouyang Q, Tandon R, Goh K-L, *et al.* The emergence of inflammatory bowel disease in the Asian Pacific region. Curr Opin Gastroenterol 2005; 21: 408-13.
10. Wright JP, Froggatt J, O'Keefe EA, *et al.* The epidemiology of inflammatory bowel disease in Cape Town 1980-1984. S Afr Med J 1996; 70: 10-5.
11. Lakatos PL. Recent trends in the epidemiology of inflammatory bowel disease: up

or down? World J Gastroenterol 2006; 14: 6102-8.

12. Loftus EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence and environmental influences. Gastroenterol 2004; 126: 1504-17.
13. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347: 417-29.
14. Comalada M, Peppelenbosch MP. Impaired innate immunity in Crohn's disease. Trends Mol Med 2005; 12: 397-9.
15. Korzenik JR, Dieckgraefe BK, Valentine JF, *et al.* Sargramostim for active Crohn's disease. N Engl J Med 2005; 352: 2193-201.
16. Gaya DR, Russell RK, Nimmo E, *et al.* New genes in inflammatory bowel disease: lessons for complex diseases? Lancet 2006; 367: 1271-84.
17. Polymeros D, Bogdanos DP, Day R, *et al.* Does cross-reactivity between *Mycobacterium avium paratuberculosis* and human intestinal antigens characterise Crohn's disease? Gastroenterology 2006; 131: 85-96.
18. Horvath KD, Whelan RL. Intestinal tuberculosis: return of an old disease. Am J Gastroenterol 1998; 93: 692-6.
19. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol 1993; 88: 989-99.
20. Akgun Y. Intestinal and peritoneal tuberculosis: changing trends over 10 years and a review of 80 patients. Can J Surg 2005; 48: 131-6.
21. Bhansali SK. Abdominal tuberculosis: experience with 300 cases. Am J Gastroenterol 1977; 67: 324-37.
22. Epstein D; Watermeyer G; Kirsch R. The diagnosis and management of Crohn’s disease in populations with high risk rates for tuberculosis. Aliment Pharmacol Ther. 2007; 25(12):1373-1388.
23. den Boon S, van Lill SWP, Borgdorff, *et al.* Association between smoking and tuberculosis infection: a population survey in a high tuberculosis incidence area. Thorax 2005; 60: 555-7.
24. Lingenfelser T, Zak J, Marks IN, *et al.* Abdominal tuberculosis: still a potentially

lethal disease. Am J Gastroenterol 1993; 5: 744-50.

25. Loftus EV, Silverstein MD, Sandborn WJ, *et al.* Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence and survival. Gastroenterol 1998; 114: 1161-8.
26. Kapoor VK. Abdominal tuberculosis. Postgrad Med J 1998; 74: 459-67.
27. Danese S, Semeraro S, Papa A, *et al.* Extra intestinal manifestations in inflammatory bowel disease. World J Gastroenterol 2005; 11: 7227-36.
28. Nagi B, Sodhi KS, Kochhar R, *et al.* Small bowel tuberculosis: enteroclysis findings. Abdom Imaging 2004; 29: 335-40.
29. Franco-Paredes C, Diaz-Borjon A, Senger MA, *et al.* The ever expanding association between rheumatologic disease and tuberculosis. Am J Med 2006; 119: 470-7.
30. Omori H, Asahi H, Inoue Y, *et al.* Pulmonary involvement in Crohn's disease: report of a case and review of the literature. Inflamm Bowel Dis 2004; 10: 129-34.
31. Verrier Jones J, Housley J, Ashurst PM, *et al.* Development of delayed hypersensitivity to dinitrochlorobenzene in patients with Crohn's disease. Gut 1969; 10: 52-6.
32. Singh V, Kumar P, Kamal J, *et al.* Clinicocolonoscopic profile of colonic tuberculosis. Am J Gastroenterol 1996; 3: 565-8.
33. Alvares JF, Devarbhavi H, Makhija P, *et al.* Clinical, colonoscopic, and histological profile of colonic tuberculosis in a tertiary hospital. Endoscopy 2005; 37: 351-6.
34. Kim KM, Lee A, Choi KY, *et al.* Intestinal tuberculosis: Clinicopathologic analysis and diagnosis by endoscopic biopsy. Am J Gastroenterol 1998; 93: 606-9.
35. Shah S, Thomas V, Mathan M, *et al.* Colonoscopic study of 50 patients with colonic tuberculosis. Gut 1992; 33: 347-51.

36. Gilinsky NH, Voigt MD, Bass DH, *et al.* Tuberculous perforation of the bowel. S Afr Med J 1986; 70: 44-6.
37. Lee YJ, Yang SK, Byeon JS, *et al.* Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy 2006; 38: 592-7.
38. Gan HT, Chen YQ, Ouyang Q, *et al.* Differentiation between intestinal tuberculosis and Crohn's disease in endoscopic biopsy specimens by polymerase chain reaction. Am J Gastroenterol 2002; 97: 1446-51.
39. Pulimood AB, Peter S, Ramakrishna B, *et al.* Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. J Gastroenterol Hepatol 2005; 20: 688-96.
40. Pulimood AB, Ramakrishna BS, Kurian G, *et al.* Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. Gut 1999; 45: 537-41.
41. Kirsch R, Pentecost M, Hall Pde M, *et al.* Role of colonoscopic biopsy in distinguishing between Crohn's disease and intestinal tuberculosis. J Clin Pathol 2006; 59: 840-4.
42. Vanhoenacker FM, De Backer AI, Op de Beeck, *et al.* Imaging of gastrointestinal and abdominal tuberculosis. Eur Radiol 2004; 14: E103-15.
43. Nagi B, Sodhi KS, Kochhar R, *et al.* Small bowel tuberculosis: enteroclysis findings. Abdom Imaging 2004; 29: 335-40.
44. Pereira JM, Madureira AJ, Viera A, *et al.* Abdominal tuberculosis: imaging features. Eur J Radiol 2005; 55: 173-80.
45. Balthazar EJ, Gordon R, Hulnick D. Ileocaecal tuberculosis: CT and radiologic evaluation. Am J Roentgenol 1990; 154: 499-503.
46. Gore RM, Balthazar EJ, Ghahremani GG, *et al.* CT features of ulcerative colitis and Crohn's disease. Am J Roentgenol 1996; 167: 3-15.
47. De Backer AI, Mortelé KJ, Deeren D, *et al.* Abdominal tuberculous

lymphadenopathy: MRI features. Eur Radiol 2005; 15: 2104-9.

48. MacKalski BA, Bernstein CN. New diagnostic imaging tools for inflammatory bowel disease. Gut 2006; 55: 733-41.
49. Ambrosinin R, Barchiesi A, Di Mizio V, *et al.* Inflammatory chronic disease of the colon: how to image. Eur J Radiol 2007; 61: 442-8.
50. Sheehan AL, Warren BF, Gear MWL, *et al.* Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. Br J Surg 1992; 79: 955-8.
51. Bhargava DK, Shriniwas Chopra P, *et al.* Peritoneal tuberculosis: laparoscopic patterns and its diagnostic accuracy. Am J Gastroenterol 1992; 87: 109-12.
52. American Gastroenterological Association Institute. Technical review on corticosteroids, immunomodulators and infliximab in inflammatory bowel disease. Gastroenterology 2006; 130: 940-87.
53. Jasmer RM, Nahid P, Hopewell PC. Clinical practise. Latent tuberculosis infection. N Engl J Med 2002; 347: 1860-6.
54. Wang L, Turner MO, Elwood RK, *et al.* A meta-analysis of the effect of Bacille-Calmette-Guerin vaccination on tuberculin skin test measurements. Thorax 2002; 57: 804-9.
55. Gardam MA, Keystone EC, Menzies R, *et al.* Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003; 3: 148-55.
56. Sichletidis L, Settas L, Spyratos D, *et al.* Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis 2006; 10: 1127-32.
57. Jasmer RM, Saukkonen JJ, Blumberg HM, *et al.* Short-course rifampicin and pyrazinamide compared with isoniazid for latent tuberculosis infections; a multicenter clinical trial. Ann Intern Med 2002; 137: 640-7.
58. Ormerod LP. BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF-α treatment. Thorax 2005; 60: 800-5.

59. Benito N, Sued O, Moreno A, *et al.* Diagnosis and treatment of latent tuberculosis infection in liver transplant recipients in an endemic area. Transplantation 2002; 74: 1381-6.
60. Jayanthi V, Robinson RJ, Malathi S, *et al*. Does Crohn's disease need differentiation from tuberculosis? J Gastroenterol Hepatol 1996; 11(2): 183-6.
61. Sato S, Yao K, Yao T, *et al*. Colonoscopy in the diagnosis of intestinal tuberculosis in asymptomatic patients. Gastrointest Endosc 2004; 59: 362-8
62. Jeong SH, Lee KJ, Kim YB, *et al*. Diagnostic value of terminal ileum intubation during colonoscopy. J Gastroenterol Hepatol 2008; 23(1): 51-55
63. Patel N, Amarapurkar D, Agal S, *et al.* Gastrointestinal luminal tuberculosis: establishing a diagnosis. J Gastroenterol Hepatol 2004; 19: 1240-6.

PROFORMA

Case No:

Demography:

Name:

Date of Regn:

Age:

MGE No:

Sex:

Address:

Per-capita income:

Literacy level:

Clinical diagnosis:

Duration of symptoms:

Smoking:

Interval between onset and diagnosis:

Alcohol:

Tobacco:

History:

Fever:

Mass abdomen:

Abdominal pain:

Pedal edema:

Chronic diarrhoea:

Anemia:

Blood and mucous stools:

Hypoproteinemia:

Perianal symptoms:
Fissure/Hemorrhoid/Abscess

Past H/o TB:
Treated for TB:

Joint symptoms:

Family H/o TB:

Skin symptoms:

H/o appendectomy:

Eye symptoms:

H/o perianal surgery:

Colonoscopic findings:

Rectal exam:

Inspection:

Palpation:

Extent of survey:

Mucosal lesions:

Isolated ileal disease:

Combined ileo-cecal involvement:

Ileo-cecal valve destruction:

Strictures:

Short segment:

Long segment:

Ulcers:

Aphthous/Serpiginous/stellate:

Circumferential:

Mucosal nodularity:

Pseudopolyps:

Skip lesions:

Cobble-stoning:

Biopsy taken from:

Colonoscopic diagnosis: C-TB/ C-CD/ C-UD

Histological diagnosis: H-TB/ H-CD/ H-IC/ H-NS